This Month in *The Journal*

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The GATES to Gene-Based Association

Li et al., page 283

Genome-wide single-SNP association analyses are powerful because they allow researchers to interrogate the entire genome at once in a hypothesis-free manner. However, as more studies have been performed, the difficulties of such an approach are becoming more prevalent. One well-recognized issue is that of dealing with the false positives associated with testing so many variants for an effect. Numerous methods have been developed to establish the best ways to correct for the enormous amount of tests, many of which are somewhat correlated. Another confounding factor is that a SNP that is found to be significantly associated with a phenotype may be a proxy SNP that is in linkage disequilibrium (LD) with a functional variant. Therefore, when LD patterns differ between populations, significant signals won't necessarily replicate. In addition, determining the mechanistic effect of associated variants can be difficult when no obvious relationship is found between a SNP and the genes nearby. A gene-based approach can be advantageous because it eliminates a large number of tests, and examining associations at the gene level provides uniformity across populations with different LD structures. Here, Li et al. present their methodology, called GATES, that can perform gene-wide association analyses by using data from millions of SNPs or sequencing data. GATES not only is capable of efficiently combining genotype data into such analyses, but it can also incorporate prior knowledge of function to give more weight to variants that are predicted to have a higher likelihood of having an effect.

Autosomal-Dominant Intellectual Disability and De Novo Mutations

Hamdan et al., page 306

The search for genetic variants that cause intellectual disability (ID) is generally more straightforward in X-linked and recessive situations because the mode of inheritance and linkage shrinks the list of potential candidate genes. Pedigrees in which ID segregates in a dominant fashion will not be as common because ID often interferes with the reproductive fitness of individuals. One way to identify dominant variants is to examine de novo mutations (DNMs), but without any way to limit the region of interest, this means that the entire autosomal genome needs to be considered. Although high-throughput sequencing techniques are becoming increasingly fast and cost-efficient, a more targeted approach can be beneficial. In this issue, Hamdan et al. focus on genes that have a high likelihood of being involved in learning and memory: genes encoding proteins that are components of synaptic glutamate receptor complexes. The authors hypothesize that variants that affect the function of these proteins would cause ID. The authors identify several DNMs in these glutamate receptor genes in individuals with ID and, through a variety of molecular approaches specific to each protein, demonstrate that the DNMs affect function.

Diversity in Duplications

Campbell et al., page 317

Copy-number polymorphisms (CNPs) are deletions or duplications of the genome larger than 1 kb that are found at frequencies greater than 1% in human populations. The less-frequent deletions and duplications are better defined as copy-number variants (CNVs). Many recent studies have utilized SNP genotyping arrays to detect CNPs and CNVs and to test for associations between these deletions and duplications and common diseases and/or traits. Although many associations have been reported, many are likely to have been missed because of SNP scarcity in genomic regions of segmental duplication (SD). CNPs and CNVs are enriched in such regions, and data suggest that deletions and duplication within SDs are highly variable in humans. Analysis of CNPs that vary in copy number between different populations will likely provide useful information regarding demographics and natural selection. However, in order to conduct such an analysis, a denser SNP array that includes SNPs within SDs is needed. In this issue, Campbell and colleagues devise such an array that can be combined with existing microarrays and examine CNPs in a number of human populations. Their data indicate that CNPs within SDs are indeed more likely to be population specific than are CNPs found outside of SDs. Closer analysis of a subset of CNPs in additional samples from 62 different populations identifies CNPs affecting specific genes of likely clinical significance. These data highlight the important role that CNPs have played in establishing and maintaining human diversity.

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CNNM2 Mutations Can Drain Your Energy

Stuvier et al., page 333

Magnesium (Mg) exists as an ion within our bodies, where it plays a crucial role in many different biological processes. Mg^{2+} acts as a coenzyme in hundreds of reactions, including the synthesis of DNA and RNA. In fact, it is required for all reactions using or synthesizing ATP, the energy source of our bodies. In addition to being a natural part of our systems, Mg compounds may be taken for aid in acute or chronic discomforts. Examples include Epsom salt (magnesium sulfate) for constipation and milk of magnesia (magnesium hydroxide) for heartburn. Mg^{2+} is found in many foods, including nuts, coffee, and spinach. Insufficient dietary intake of Mg^{2+} may cause hypomagnesemia, an electrolyte disturbance in the blood. Hypomagnesemia may also be caused by excess loss or inefficient absorption of Mg^{2+} due to chronic diarrhea, alcoholism, or stress. It can also occur as a familial genetic disorder. Symptoms of this condition include muscle cramps (tetany), cardiac arrhythmia, and seizures. Mutations in several genes have been found to cause recessive and dominant forms of familial hypomagnesemia. In this issue, Stuvier and colleagues use an interesting approach to identify mutations in another gene that cause Mg^{2+} wasting. Using expression data from a mouse model of Mg^{2+} wasting combined with frog data and additional mouse data, this group identifies *CNNM2* as a candidate for harboring mutations causing Mg^{2+} transport deficiencies. Sequence analysis of *CNNM2* in two unrelated families suffering from dominant hypomagnesemia reveals two separate mutations in this gene, definitively adding CNNM2 to the list of proteins regulating renal reabsorption.

A Search for Variants Associated with Bipolar Disorder

Cichon et al., page 372

Genome-wide association studies have not been all that successful in identifying variants associated with neuropsychiatric disorders. In the case of bipolar disorder (BD), large meta-analyses have detected a few consistent signals, but even those associations that have been found in multiple data sets do not always meet the strict standards for significance. In this issue, Cichon et al. report the results of their effort to identify additional genetic variants that are associated with BD risk. By analyzing samples from thousands of individuals, the authors are able to detect a significant association with a variant in neurocan (*NCAN*). As the gene name might suggest, previous work has shown expression in the brain, and the authors perform additional expression work here in mice and in human tissues to look at specific regions. The results are encouraging in that *Ncan* is expressed in cortical and hippocampal areas and *NCAN* is highly expressed in the human hippocampus; these regions have been implicated previously as sites of dysfunction in individuals with BD. There is an *Ncan*-deficient mouse model as well, in which future evaluations may reveal BD-related phenotypes.